

**R E M A R K S**

In the present Application, Claims 1, 7, 13 and 19 have been amended and Claims 5, 11, 17 and 23 have been cancelled. As such, Claims 1-4, 6-10, 12-16, 18-22 and 24 are currently pending. The Examiner's rejections are as follows:

- I. Claims 1, 3-7, 9-13, 15-19, 21-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Aruffo ('693 patent).
- II. Claims 1-24 stand rejected under 103(a) as allegedly obvious in light of Jones *et al.* (Nature paper) and further in view of Yelton *et al.* (The Journal of Immunology 155:1994-2004 [1995]) and Soderlind *et al.* (Gene paper) and Hagiwara *et al.* (US Patent No. 5,589,573, issued Dec. 31, 1996).
- III. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being obvious in light of Aruffo ('693 patent) and further in view of Hagiwara.
- IV. Claims 1-24 stand rejected under 35 U.S.C. 102(f) in light of the Watkins 1.131 Declaration.

**I. Aruffo et al. Rejection Under 102(e)**

The Examiner rejected Claims 1, 3-7, 9-13, 15-19, and 21-24 under 35 U.S.C. 102(e) as being anticipated by Aruffo et al. (U.S. Pat. 6,312,693). The Examiner indicated that the 1.131 Declaration of Dr. Watkins was not deemed persuasive in removing this rejection (Office Action page 2). While Applicants disagree with the Examiner's position and believe the 1.131 Declaration (filed in accordance with MPEP 715) is sufficient to remove Aruffo et al. as a reference, Applicants have concluded that a CFR 1.132 Declaration may be more appropriate in this situation to expedite prosecution. As explained below, a 1.132 Declaration addressing the Aruffo patent has previously been filed in a related Application.

In Serial Number 09/434,870 (AME-06352), on April 30, 2002, Applicants filed 1.132

Declaration by Dr. Watkins in conjunction with a Supplemental Information Disclosure Statement that listed the Aruffo patent. This 1.132 Declaration supplied the necessary "unequivocal statements" as required under MPEP 716.10 to prevent the Aruffo patent from being cited as a 102(e) prior art reference.<sup>1</sup>

Applicants have attached a copy of this 1.132 Declaration at Tab A to the present communication. This Declaration provides the proper unequivocal statements in accordance with MPEP 716.10 to remove the Aruffo reference as a citable 102(e) reference (i.e. this Declaration carefully tracks the requirements of MPEP 716.10 and is more than sufficient to remove the Aruffo reference). In light of this 1.132 Declaration, the 102(e) rejection under Aruffo must be withdrawn.

## **II. Claims 1-24 Are Not Obvious**

The Examiner alleges that the claims are obvious and unpatentable over Jones *et al.* and further in view of Yelton *et al.* (The Journal of Immunology 155:1994-2002 [1995]) and Soderlind *et al.* (Gene paper) and Hagiwara *et al.* (US Patent No. 5,589,573). Applicants disagree as the Examiner has failed to establish a *prima facie* case of obviousness (*see* previous Response dated August 11, 2003, herein incorporated by reference).

The Examiner originally cited the Jones *et al.* reference as teaching the use of donor CDRs with an acceptor framework. The Examiner attempts to make up for Jones *et al.* lack of teaching modified CDRs by citing the Yelton *et al.* and Soderlind *et al.* references. For example, the Examiner states:

"It would have been obvious at the time of the Yelton reference to apply affinity maturation to the antibody of Jones to obtain better binding affinity for therapy and humanization as taught by Yelton." (Office Action, page 3).

The Yetlton *et al.* and Soderlind *et al.* references, however, do not remedy the deficiencies of the Jones *et al.* reference as the CDR modifications discussed in these two references are NOT in the **donor/acceptor** context.

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<sup>1</sup> It is noted that the Examiner in Ser. No. 09/434,870 (the same Examiner as in the present case) after being made aware of the Aruffo patent in the Supplemental IDS, did not cite the Aruffo patent in two subsequent Office Actions. However, over a year later, the Examiner did cite the Aruffo patent as 102(e) art, apparently unaware that the 1.132 Declaration had been filed with the Supplemental IDS (*see* Office Action dated 4/29/03). Applicants Response to this Office Action did not note that a 1.132 Declaration had been filed properly addressing the Aruffo reference, but instead filed a 1.131 Declaration that the Examiner has since objected to as not being persuasive.

Neither the Yelton et al. or Soderlind et al. references employ ANY TYPE of **acceptor** frameworks.<sup>2</sup> Instead, the CDR modifications discussed in Yelton et al. and Soderlind et al. are made in the ORIGINAL variable region which contains the original framework (i.e. they are employing donor frameworks with donor modified CDRs, so they are in the donor/donor context, not the donor/acceptor context as in the present claims). As the Examiner is undoubtedly aware, using DONOR frameworks and modified DONOR CDRs eliminates the giant hurdle posed by using a non-donor (acceptor) frameworks since the non-donor frameworks are highly unlikely to present the modified donor CDRs in the same conformation<sup>3</sup> as the DONOR framework.

Since the Yelton et al. and Soderlind references are only concerned with changing the CDRs in a donor variable region, and NOT concerned with ALSO swapping out the entire framework with a different (acceptor) framework, it is clear the one would not be motivated to combine these references with the Jones et al. reference as required to establish a *prima facie* case of obviousness. Moreover, nothing in these references suggests (as required to establish a *prima facie* case of obviousness) that one could reasonably expect to successfully combine the Yelton et al and Soderlind et al. references with the Jones et al. reference. As such, the Examiner has not established a *prima facie* case of obviousness.

Nonetheless, for business reasons, in order to further the prosecution of the present Application, yet without acquiescing to the Examiner's rejection, while explicitly reserving the right to prosecute the original claims (or similar claims) in the future, Applicants have canceled certain claims and amended certain claims. In particular, Applicants have amended Claims 1, 7, 13 and 19 by specifying that the "donor framework regions" and "donor complementarity-determining regions" are **non-human**, and specifying that the "acceptor framework regions" are **human**. These amendments serve to further underscore the deficiencies of the Yelton and Soderlind references which don't even teach using an acceptor framework from the same species (e.g. an acceptor murine sequence), let alone using an acceptor from a totally different species

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<sup>2</sup> Soderlind et al., "Experimental and Discussion" page 270 indicates that no attempt was made to use an acceptor framework from a different variable region. Instead, the frameworks from the variable region that is the original source of the CDRs is employed. Yelton et al., see "Material and Methods" pages 2005-2006 which indicates that the source of the CDRs (to be modified) and the framework that is used are from the same original variable region (i.e. no acceptor is used, instead, the CDRs are simply being mutated in a variable region).

<sup>3</sup> See, *The Encyclopedia of Molecular Biology*, Ed. Sir John Kendrew, Blackwell Science, 1994, page 384. which states "[f]ramework regions determine the three-dimensional structure of the V region ensuring that the CDRs are brought into the correct steric relationship with each other."

(i.e. human acceptor frameworks regions). As such, the patentability of the amended claims is clear and they should be immediately passed to allowance.

### **III. Aruffo et al. and Hagiwara Obviousness Rejection**

The Examiner has rejected Claims 1-24 under 35 U.S.C. 103(a) as being unpatentable over the Aruffo et al. patent and Hagiware et al patent. (Office Action pages 5-6). In light of the attached 1.132 Declaration, it is clear that the Aruffo et al. patent cannot be cited by the Examiner. As such, Applicants respectfully submit that this rejection is moot.

### **IV. 35 U.S.C. 102(f) Rejection**

The Examiner has rejected Claims 1-24 under 35 U.S.C. 102(f) alleging that the Applicants did not invent the claimed subject matter. In particular, the Examiner states that:

"Because of the declaration filed 8/13/03 by Dr. Watkins stating that **he performed the work** of the overlapping oligonucleotides and cites evidence in the comparison between various pages in the application and the patent of Arruffo, it is now unclear due to the statement in the declaration that Dr. Watkins **invented the oligo work** what the contributions of the other two inventors, Dr. Huse and Dr. Wu were." (*emphasis added*, Office Action, page 6).

Applicants submit that a careful reading of the 1.131 Declaration, and applying correct inventorship law, moots this rejection.

The Examiner appears to assert that Dr. Watkins was the only person to perform the cited work. Applicants note that the 1.131 Declaration actually says "[t]he overlapping oligonucleotide work described in pages 54-55 of the present specification was performed by me or was done under my supervision .." (Watkins 1.131 Declaration page 2, lines 1-2). As such, it is clear that Dr. Watkins never asserted he alone performed all of the work as alleged by the Examiner.

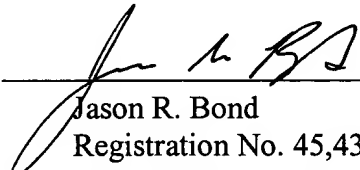
Second, the Examiner indicates that the Watkins 1.1.31 Declaration asserts that Dr. Watkins "invented" the oligo work. No such statement is present in the Declaration (again, see page 2, lines 1-2). In fact, the 1.131 Declaration does NOT discuss inventorship. Applicants remind the Examiner that inventorship relates to who *conceived* of the invention, not who actually reduced it to practice. The 1.131 Declaration does not comment on who invented the oligo work.

In light of the Examiner's mis-reading of the 1.131 Declaration, it is clear that there is no 102(f) issue as alleged by the Examiner. Moreover, it is noted that the newly submitted 1.132 Declaration (dated April 25, 2002) DOES address inventorship, making affirmative statements that Dr. Watkins, Dr. Huse and Dr. Wu were the sole inventors of the oligo work (and not the other inventors listed on the front page of the Aruffo patent). As such, it is clear that this 102(f) rejection should be withdrawn immediately.

### CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants' claims should be passed to allowance. If the Examiner believes an interview would help expedite the allowance of this case, Applicants ask the Examiner to please call the undersigned at 608-218-6900.

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